The Virtual Physiological Human Institute
Actions for Horizon 2020 projects

1. Introduction

The Virtual Physiological Human institute (Belgian non-for-profit, http://vph-institute.org) is an open community of scientists, clinicians focused and other healthcare professionals, focusing on the development and uptake of computer modeling & simulation in healthcare. VPHi represents many of the largest in silico medicine research groups worldwide. It has established collaborations with many sister societies and organizations (e.g. ESB (biomech), JRC, CAAT etc). Besides the organization of typical scientific society activities such as a bi-annual conference, summer schools, webinars and mentoring activities, the VPHi has also been very active in policy development and stakeholder interaction. These activities have been enhanced through the establishment of a formal collaboration in equal partnership with software, device and pharmaceutical industry: the Avicenna Alliance (also Belgian non-for-profit, http://avicenna-alliance.com). Examples of these policy and stakeholder activities are the introduction of in silico modeling into the Medical Device Regulation and the legislation of the European Medicines Agency. Recent activities are focusing on establishing proper regulation for the use of computer modeling and simulation in all medical applications. Hereto, an active partnership with FDA and EMA has been formed. The VPHi is currently leading, together with EMA, the writing of a white paper with guidelines on the validation of computer models used in the context of drug development. Additionally, the VPHi is actively interacting with members of the European Commission (DG CNECT & RTD) to provide state-of-the-art success stories on the use of computer modeling and simulation to advance healthcare and to discuss the challenges ahead to further facilitate in silico medicine.

Participation of the VPHi in any Horizon 2020 consortium can focus on one or more of the following core activities

- Communication & dissemination
- Stakeholder assessment & outreach
- Regulatory & Policy

Currently the Institute is already partner of 3 (out of 4) projects funded under the call "Accelerating the uptake of computer simulations for testing medicines and medical devices" taking care of a mix of the activities mentioned above:

- In silico world - insilico.world

- SimCardioTest - www.simcardiotest.eu

- SimCor - www.simcor-h2020.eu

2. Communication and dissemination

Established tools within the VPH institute are the following.

- The VPHi is the owner of the VPH conference brand. This biannual event has been running since 2010, and over the years has been growing its importance and outreach potentials. The last conferences were organized by Inria (Paris) in 2020 as an on line event (600 delegates) and Zaragoza in 2018 (250 delegates). The upcoming conference will be in Porto- Portugal on 6/9 September 2022 and will focus on "Digital twins for personalized treatment development and clinical trials". More information can be found here: http://vph-conference.org/
- A monthly e-newsletter which reaches 7.000 unique contacts related to in silico medicine world
- A webinar series, organized since 2016 by the VPHi student committee that features prestigious keynote speakers on specific research topics related to in silico medicine.
- Social network presence: LinkedIn, Twitter, YouTube
- An established institutional website

The VPHi is available to join future funded EC projects taking care of dissemination activities and community engagement/building exercises, such as:

- Production and distribution of the communication material through all its channels
- News items and events, press releases, brochures etc.
- Monthly e-newsletter
- Printed newsletter on regular bases (i.e. every 6 months)
- Project video
- Organization of on line webinars on project topics

3. Stakeholder engagement and outreach

A number of important stakeholders are involved in the in silico medicine world:

- Clinical community (the actual end- user of VPH technologies)
- Industry (the producers of products that are based on VPH technologies)
- Health Technology Assessment organizations (assessing in silico medicine products)
- Payers & Insurance companies (possible reimbursement of in silico medicine related costs)
- Citizen and Patient organizations (who represents the patients that could (or already) benefit from the use and application of VPH technologies)
- Institutional community (funding bodies, regulators…), who regulates and shapes the future of in silico medicine

The VPHi is in contact with many of these stakeholders already – either through the engagement of their representatives of these stakeholders within the institute itself, or through collaborations. Through these representatives and through the entire VPHi membership, contacts have been/can be made with larger organizations representing these categories on a higher level.

When doing stakeholder engagement and outreach, an important pillar in the realization of Responsible Research & Innovation [3], specific programs should be set up, tailored to each

of the stakeholder categories. For every stakeholder, a similar structure will be followed, although the specific implementation will differ for the different groups. First, a desk review will be conducted to get a good view on the state-of-the art of uptake and use of in silico medicine in a particular group as well as to identify possible partner organization for each stakeholder group (e.g. professional organizations, networks, existing event). This will be followed by an assessment where the stakeholder group will be interrogated to identify knowledge gaps, perceived risks and hurdles. This assessment can be done in the form of semi-structured interviews, panels, focus groups or questionnaires. This information will be analyzed to distill key actions to be taken and discussed with the consortium in order to identify specific opportunities to link the identified actions to developments within the project. Subsequently these actions will be implemented in a format that is tailored to the specific target group which can include the creation of instructive video's, the development of a lecture series and the drafting of a (targeted) road map. Finally, the impact of the actions will be evaluated through another round of interviews, focus groups etc. and follow-up actions identified where necessary.

4. Regulatory & Policy

Policy

As mentioned previously, in collaboration with industry partners in the context of the Avicenna Alliance, the VPHi has had impact on the Medical Device Regulation and the current EMA legislation. Currently, the pediatric and orphan medicine regulation are under review (or will be soon) and actions are being planned to lobby for the inclusion of specific references to computer modeling & simulation in those regulations. In clusion of such explicit reference to CM&S will provide a mandate to companies, academics and all parties involved in the respective fields that are using CM&S in the search for safer and cheaper treatments for these categories of patients that are often overlooked by mainstream developments.

This process starts with the formation of an expert working group within the VPHi/Avicenna Alliance with representation from both academia, industry and other relevant stakeholders. This working group drafts a white paper, detailing the current state of the art as well as the possibilities that explicit inclusion of CM&S in the regulation can provide (see [4] for example on medical devices). Examples will be provided in said white paper, as well as a number of challenges to be addressed. Specific training or information events can be provided to the relevant policy makers to suggest tangible actions and amendments to the regulations.

Regulatory

In order for digital evidence (evidence generated via the use of computer modeling & simulation) to be admitted as genuine evidence in a regulatory submission, or in order for computer models to obtain qualification as a tool, a thorough validation process needs to be followed. This can be summarized by VVUQ: verification, validation and uncertainty quantification [5]. Verification refers to the agreement between the mathematical model and the simulation results (both at the level of the model and the code). Validation refers to the agreement between the simulation results and the physical reality (impacted by the way the

measures used to assess this agreement, as well as the quality of the physical data used as a comparator). Uncertainty Quantification relates to the assessment of the impact uncertainty on model assumptions and parameters has on the model's behavior, within the predefined context of use. A good overview of the history and relevant regulatory documents can be found in [6].

FDA has been very instrumental in driving the inclusion of in silico models in regulatory submissions for medical devices, starting with the publication of specific documentation guidelines [7]. After and thorough process with involvement of FDA and industrial partners, an ASME standard was released in 2018 (VV-40-2018 [8]) related to the verification and validation of computer models in the development of medical devices. The standard relates the amount of V&V that is required to pass regulatory scrutiny to the risk related to the use of the model (risk is defined as a combination of the influence the model has on the medical decision and the consequence of an error for the patient). At the European level, EMA regulations on physiology-based pharmacokinetic models used frequently in drug development [9], follow a comparable verification and validation strategy. VPHi and EMA have recently joined forces to develop guidelines to go towards a validation strategy for all types of in silico medicine models [ref]. Besides regulators and academia, the working group can count on the active participation of industry and other healthcare professionals. Once the general guidelines have been published, specific implementation of said guidelines in the application area of the project should be established. VPHi will guide this process ensuring the engagement of the relevant stakeholders.

5. Budget

In general terms, EC funded projects allocate a 10-15% of their total budget to dissemination and exploitation activities.

For a 4 million EC projects this means an allocation of 400.000 to 600.000 over the whole project.

- Dissemination: €30.000 per year for each project year
- Community engagement and outreach: the budget should vary in connection to the scope of the projects and could go from €50.000 to €300.000 in total, distributed over the aforementioned activities.

References

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[3] https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation

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[5] Pathmanathan P, Gray RA, Romero VJ, Morrison TM. Applicability analysis of validation evidence for biomedical computational models J. Verif. Valid. Uncert., 2 (2) (2017)

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[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions.

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[9] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf.